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F.F. and L.Q.-M. contributed equally to this work.

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To the editor:

Bridging to transplant with azacitidine in juvenile myelomonocytic leukemia: a retrospective analysis of the EWOG-MDS study group

DNA methyltransferase-inhibiting azanucleosides have become a mainstay of treatment of myeloid neoplasms in adult patients,[1] with 5-azacytidine (azacitidine) being the agent in broadest clinical use. Although not curative, treatment with azacitidine achieves hematologic improvement and transfusion independency in many patients and prolongs survival.[2,3] Even though most children with juvenile myelomonocytic leukemia (JMML) qualify for allogeneic hematopoietic stem cell transplantation (HSCT), the acceptable toxicity of low-dose azacitidine and its cytoreductive potential make it an attractive option as a bridging therapy before HSCT[4] or as palliation after 1 or more transplants have failed. We previously published the first case report of a boy with JMML who achieved a complete clinical and genetic remission after 8 cycles of azacitidine.[5] Here, we present a retrospective compilation of 12 children with JMML who received individual off-label treatment with azacitidine before HSCT (N = 9) or for relapsed disease (N = 3).

The children were treated at 11 centers November 2007-April 2012. Ten children were enrolled in the studies "98" or "2006" of the European Working Group of Myelodysplastic Syndromes in Childhood (EWOG-MDS; registered at www.clinicaltrials.gov as #NCT00047268 and #NCT00662090). Approval was obtained from the institutional review board of each institution, and parental informed consent was provided according to the Declaration of Helsinki. Two children were treated at centers not participating in EWOG-MDS studies. One case (D644) was published previously.[5] The diagnosis of all children was centrally reviewed, and response was evaluated according to international consensus criteria.[6]

The median age of the 12 patients was 4.8 years (range 0.4-9.1) (Table 1). A total of 64 azacitidine cycles were administered (median 5.5 cycles, range 1-11). Seven of 12 treatments consisted of 100 mg/m^2 azacitidine per intravenous infusion on 5 consecutive days every 28 days. In the other 5 patients, the substance was administered over 5 to 7 days at a single dose of 50 to 100 mg/m^2 per intravenous or subcutaneous route every 28 to 42 days.

Severe neutropenia ($\leq$500/μL) was observed in 4 children. Cytopenias led to dose reduction in 2 children, both treated for relapse after second HSCT. Other adverse events were gastrointestinal problems including nausea and vomiting in 2 children, skin rash in 2 children, and fatigue or slight creatinine elevation in 1 patient each. Seven episodes of infection were reported for a total of 64 azacitidine cycles (10.9%).

Of 9 children treated prior to HSCT, 3 normalized blood counts and spleen size (scored as clinical CR) (Table 1). In 2 of these patients, monosomy 7 was present in leukemic cells but disappeared after cycles 5 and 6, respectively. The leukemic karyotype was normal in the other child with clinical CR, precluding the assessment of cytogenetic response. Two of the 3 CR patients featured a somatic *PTPN11* gene mutation. The mutation became undetectable after cycle 6 in 1 child (NS002); material for mutational analysis under azacitidine was unavailable from the other child (D827). The third leukemia carried a somatic *KRAS* mutation, which was no longer detectable after 7 cycles of azacitidine (D644).[5] One child (CH058) experienced considerable regression of spleen size and became transfusion independent (scored as clinical PR). All 4 children underwent HSCT after 7 to 11 cycles. A fifth child (NS001) responded unusually early, as indicated by reduction of splenomegaly after the first cycle and hematologic improvement after cycle 3 (scored as clinical PR). Azacitidine was then discontinued because of parental choice. Three children progressed rapidly under azacitidine and underwent expedited HSCT. One child (I255) was not evaluable for response because of concomitant treatment. Three children with JMML received azacitidine for leukemia recurrence after the second HSCT. They achieved clinical PR or could be maintained in stable disease for 4 cycles before progressing.

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Table 1. Response to azacitidine in children with JMML

Disease status	Patient identifier	Age (y) and gender	Cytogenetics	Mutational group*	Azacitidine cycles	Concomitant treatment	Response to azacitidine†	HSCT (total number)	Status	Follow-up (mo)‡
Prior to first HSCT	A062	1.1, male	Del(5)(q13q33)	*NRAS*	1 2-3	None None	PR PD	Yes (2)	Alive with leukemia	38
Prior to first HSCT	CH058	2.8, male	Normal	*PTPN11*	1-3 4-7	None None	SD PR	Yes (2)	Alive with leukemia	16
Prior to first HSCT	D644§	1.4, male	−7	*KRAS*	1 2-4 5-8	None None None	PD SD CR‖	Yes (1)	Alive in remission	62
Prior to first HSCT	D706	5.9, male	−7	*PTPN11*	1	None	PD	Yes (3)	Alive in remission	66
Prior to first HSCT	D712	6.3, female	Normal	*NRAS*	1	None	PD	Yes (1)	Dead, TRM	1
Prior to first HSCT	D827	0.4, male	Normal	*PTPN11*	1-2 3-7	6MP None	Not evaluable CR¶	Yes (1)	Alive in remission	38
Prior to first HSCT	I255	9.1, male	Inv(2)(p23q13), −7	No mutation	1-4	AraC, 6MP	Not evaluable	Yes (1)	Alive in remission	49
Prior to first HSCT	NS001	5.4, male	−7	*NRAS*	1-3	None	PR	No	Dead, progressive disease	No data
Prior to first HSCT	NS002	0.8, male	−7	*PTPN11*	1 2-3 4-11	None None None	SD PR CR#	Yes (1)	Dead, TRM	13
Relapse after HSCT**	NL121	4.6, male	Not done	*PTPN11*	2-4 1, 5-8	None None	SD PD	Yes (3)	Dead, third relapse	6
Relapse after HSCT**	SC108	5.0, male	Normal††	*NF1*	1-2 3-4 5	None None None	SD PR PD	Yes (2)	Dead, progressive disease	1
Relapse after HSCT**	SC156	5.3, male	Normal††	*PTPN11*	2-4 1, 5-6	None None	PR PD	Yes (3)	Dead, third relapse	5

AraC, cytarabine; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; 6MP, 6-mercaptopurine; TRM, transplantation-related mortality.

*All mutations were confirmed to be somatic. Neurofibromatosis type 1 was diagnosed clinically.

†Cycles of azacitidine with concomitant antineoplastic medication were considered not evaluable.

‡From the end of azacitidine treatment to death or last follow-up.

§This case was published previously by Furlan et al.[5]

‖The patient reached genetic CR with disappearance of monosomy 7 and *KRAS* mutation after 5 and 7 cycles, respectively. Monosomy 7 was tested by fluorescence in situ hybridization, and *KRAS* mutation was assessed by Sanger sequencing.

¶Material for mutational studies was not available at the time of clinical CR.

#The patient reached genetic CR with disappearance of monosomy 7 and *PTPN11* mutation after 6 cycles. Monosomy 7 was tested by fluorescence in situ hybridization, and *PTPN11* mutation was assessed by Sanger sequencing.

**Relapse after second HSCT.

††Last cytogenetic analysis: SC108, at start of azacitidine treatment; SC156, prior to second HSCT.

In summary, this retrospective series indicates that low-dose azacitidine is effective and tolerable in JMML and documents 3 cases of JMML where azacitidine induced complete clinical, cytogenetic, and/or molecular genetic remissions before allogeneic HSCT. Importantly, complete remissions without HSCT have not been documented for JMML thus far, regardless of whether conventional cytostatic chemotherapy or newer experimental agents were applied.[7-10] Prospective clinical investigation of azacitidine, such as the ongoing collaborative Innovative Therapies in Childhood Cancer/EWOG-MDS phase 1/2 trial (Eudra-CT 2010-022235-10), is needed to clarify these questions.

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